UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF INDIANA
INDIANAPOLIS DIVISION

UNITED STATES OF AMERICA	)	
	)	
Plaintiff,	)	
	)	Cause No. _____
v.	)	
	)	21 U.S.C. §§ 331(a), 333(a)(1), 352(f)(1)
ELI LILLY AND COMPANY	)	
	)	
Defendant.	)	

INFORMATION

THE ACTING UNITED STATES ATTORNEY CHARGES THAT:

GENERAL ALLEGATIONS

At all times material to this Information, unless otherwise alleged:

BACKGROUND

1. ELI LILLY AND COMPANY (hereinafter "ELI LILLY") was a corporation operating and existing under the laws of the State of Indiana, with headquarters and manufacturing facilities located in Indianapolis, Indiana, within the Southern District of Indiana. ELI LILLY was engaged in the development, manufacture, promotion, sale, and interstate distribution of pharmaceutical drugs intended for human use. ELI LILLY distributed pharmaceutical drugs or directed the distribution of pharmaceutical drugs from the Southern District of Indiana to all fifty states, the District of Columbia, and all United States Territories.

2. The Federal Food, Drug, and Cosmetic Act ("FDCA"), *inter alia*, governed the interstate distribution of drugs for human use as codified in Title 21, United States Code, Section 301 et seq. The FDCA, and its implementing regulations, required that before a new drug may

legally be distributed in interstate commerce, a sponsor of a new drug must receive approval of a New Drug Application ("NDA") submitted pursuant to 21 U.S.C. § 355.

3. The FDCA required, at 21 U.S.C. §§ 331(d) and 355(b), that the sponsor of an NDA submit to the United States Food and Drug Administration ("FDA"), as part of the NDA, labeling for all proposed intended uses for the drug which includes, among other things, the conditions for therapeutic use. The NDA must also provide, to the satisfaction of FDA, data generated in randomized and well-controlled clinical trials that demonstrate that the drug will be safe and effective when used in accordance with the proposed labeling.

4. The FDCA, at 21 U.S.C. § 355(a), prohibited the introduction into interstate commerce of any new drug, unless an approval of an application was effective. Only after the application, including the proposed labeling, was reviewed and approved by the FDA, was the sponsor permitted by law to promote and market the drug, and only for the medical conditions of use specified in the approved labeling, for which use FDA found sufficient evidence of safety and effectiveness. Uses not approved by FDA and not included in the drug's approved labeling, were known as unapproved uses or off-label uses.

5. The FDCA, and the regulations promulgated thereunder, required that in order to label or promote a drug for a use different than the conditions for use specified in the approved labeling, the sponsor must have submitted the newly proposed indications for use and evidence, in the form of randomized and well-controlled clinical studies, sufficient to demonstrate that the drug was safe and effective for the newly proposed therapeutic use or uses. Only upon receiving approval from the FDA could the sponsor label or promote the drug for the new intended use or uses.

6. The FDCA, at 21 U.S.C. § 352(f)(1), provided that a drug is misbranded if, among other things, the labeling does not bear adequate directions for use. Adequate directions for use could not be written for medical indications or uses for which the drug had not been found by FDA to have been proven to be safe and effective through well-controlled clinical studies. Drugs that were promoted for uses that had not been approved by FDA were deemed misbranded as a matter of law under Section 352(f)(1).

7. The FDCA, at 21 U.S.C. §§ 331(a) and 331(k), prohibited the distribution in interstate commerce of a misbranded drug.

8. On or about June 8, 1997, ELI LILLY submitted an NDA seeking approval of a drug called Evista (also known by the chemical name raloxifene hydrochloride), which was a new drug within the meaning of 21 U.S.C. § 321(p) and 21 C.F.R. § 310.3(h)(4) and (5). In that application, ELI LILLY sought to demonstrate the drug's safety and efficacy for, and sought approval for, Evista's use as therapy to prevent osteoporosis in postmenopausal women. In its application, ELI LILLY also sought approval for language in the "Indications and Usage" section of the label that "there was a statistically significant reduction in the frequency of newly diagnosed breast cancer in raloxifene-treated women compared to placebo."

9. On or about September 25, 1997, ELI LILLY was informed by the FDA that FDA rejected ELI LILLY's request to include language in the product label with respect to newly diagnosed breast cancer. FDA informed ELI LILLY that: "[i]n reviewing the proposed label for raloxifene as an agent that is indicated for the prevention of osteoporosis, it is not acceptable to include language elsewhere in the label that 'there was a statistically significant reduction in the frequency of newly diagnosed breast cancer in raloxifene-treated women compared to placebo.'

Acceptance of this claim would effectively provide the sponsor with a second indication for raloxifene without review by the Division of Oncology Drug Products or the Oncologic Drugs Advisory Committee."

10. On or about December 9, 1997, FDA approved Evista to prevent osteoporosis in postmenopausal women. This approved use for Evista will be referred to throughout this Information as the "Approved Use."

11. As part of its initial NDA, ELI LILLY only submitted information that demonstrated the safety and efficacy of Evista for the prevention of osteoporosis in postmenopausal women. Evista was not approved for any therapeutic use other than the prevention of osteoporosis in postmenopausal women. Further, Evista was not, pursuant to 21 U.S.C. § 355(i), exempt from the prohibition of introducing into interstate commerce a new drug for medical indications beyond the conditions prescribed, recommended, or suggested in the approved labeling thereof.

12. As described in this Information, beginning as early as May 17, 1998, and continuing thereafter until December 4, 1998, Unapproved Uses for Evista were promoted by ELI LILLY's Evista Brand Team (the group within ELI LILLY responsible for developing the marketing and promotional messages for Evista in the United States) and ELI LILLY sales representatives promoting Evista. Such Unapproved Uses were the prevention and reduction in the risk of breast cancer and the reduction in the risk of cardiovascular disease. These Unapproved Uses for Evista will be collectively referred to in this Information as the "Unapproved Use(s)."

13. ELI LILLY did not file a new NDA or supplemental NDA seeking FDA approval

for the Unapproved Uses during the time period addressed in this Information. To date, FDA has not approved Evista for the Unapproved Uses.

14. On or about February 18, 1997, before ELI LILLY submitted its NDA for Evista to FDA, ELI LILLY "conducted a security analyst meeting for sell side analysts" in New York. According to an ELI LILLY memorandum the following day, three ELI LILLY representatives at the meeting "focused on our women's health initiatives," including Evista. Following the meeting, an analyst with Smith Barney noted "LLY'S NEXT BLOCKBUSTER: raloxifene (EVISTA)." The ELI LILLY memorandum noted that the meeting "generated the kind of excitement which you would expect. LLY traded up over $1½ following the meeting."

15. In or about February 1998, ELI LILLY's Women's Health Business Unit forecast that Evista sales would be $401 million in the United States in calendar year 1998, $750 million in 1999, and $930 million in 2000.

16. In or about April 1998, ELI LILLY's Evista Brand Team held a meeting with an independent communications consultant. According to a memorandum summarizing the meeting's results, the objectives of the meeting were to "examine the current market environment, post-launch, and to evaluate the problems from the physicians' perspective and implementation challenges from the representatives' perspective. The discussion resulted in the identification of key issues that were seen as barriers to the full adoption of Evista." A memorandum by the communications group summarized one of the issues:

> "Based on the market research, physicians perceive Evista to be less efficacious than HRT [hormone replacement therapy] or alendronate . . . It is essential to elevate the efficacy image of Evista. . . . Frame effectiveness around a specific patient. For example, rather than a 'constellation of symptoms' describe for the physician a 'constellation of needs' such as prevention of osteoporosis, prevention of cardiovascular complications, prevention of breast cancer."

17. On or about May 6, 1998, at a meeting of ELI LILLY's Raloxifene Advisory Board, a paid outside advisor who served as a member of the Board "recommended publishing the data on breast cancer and pursuing an off-label use."

18. On or about July 6, 1998, a member of ELI LILLY's Evista Brand Team sent an email message along with a slide presentation on "sales issues" to colleagues within ELI LILLY. The slide presentation noted with respect to Field Sales Issues that:

> "No sense of urgency around prevention of osteoporosis. Not enough data on fracture, breast or lipids for Evista. Not enough thoughtleader support, especially OB-Gyns. No Evista long-term safety data. Belief that HRT is 'better' for patients: multiple benefits such as cognitive function, etc. Inability to identify 'right' patient."

The next slide identified Evista Repositioning, and stated:

> "Away from 'bone plus' to women's health drug. More aggressive, first line approach. Focuses on what Evista does, not what it doesn't do. In testing, new position drew more interest from women and MDs."

The last slide stated Evista's Value Proposition, which was described as:

> "Evista is the only single agent proven to safely protect women after menopause against three of the most serious threats to their health and independence: osteoporosis, breast cancer, and cardiovascular disease."

19. On or about July 15, 1998, ELI LILLY's Evista Brand Team analyzed Evista's performance in the market. The document, entitled "ST [Short Term] update July 98," stated:

> "What is the market? The market doesn't exist today. We need to build it. The market will be defined as postmenopausal health protection with a focus on osteoporosis, cardiovascular disease, and breast cancer. . . . What is the Evista Message? Evista addresses three significant needs of women after menopause: prevention of osteoporosis, improves lipid profile, addresses concerns about breast cancer. What is Evista's competitive advantage? Best combination in a single agent for broad postmenopausal health protection. What is meant by the best combination? EFFICACY: broad efficacy in bone, breast, heart. SAFETY: safe in breast and uterus. EASY TO COMPLY: dosing, ease of use, one-pill, no breast tenderness, no bleeding."

20. In or about July 1998, ELI LILLY's Evista Brand Team initiated a "3 combined benefits" message for ELI LILLY sales representatives promoting Evista to use with doctors. At July 1998 district sales meetings for ELI LILLY sales representatives, the Evista Brand Team explained the change from "osteoporosis only" to the "the 3-Way Benefit":

> "Market research clearly indicates that OBGYNs, PCPs [Primary Care Physicians], and consumers have a significantly more positive response with a broader profile. Successful selling requires a focus on the combined benefits of Evista versus individual attributes."

21. In or about August 1998, ELI LILLY's Evista Brand Team in a 1999 Business Plan noted: "Where We've Been: Op-only [Osteoporosis only], No significant data, Market confusion, No urgency for prevention, Niched as 2nd-line, No strong support from thought leaders, Inconsistent DTC [direct to consumer advertising], Inconsistent internal positioning. Result: inferior sales." The 1999 Business Plan then noted a change in positioning to the "3-way benefit."

22. In or about October 1998, ELI LILLY's Evista Brand Team 1999-2001 Business Plan indicated a reduction in the forecast of 1998 Evista sales from $401 million to $120 million. The overview noted that "Disappointing year versus original forecast." Under the heading "Evista: Significant Learning-based Changes," the Business Plan noted a change in positioning to: "3 combined benefits versus Osteoporosis only." One of the "Strategic Marketing Objectives" set forth in the Business Plan was to "Build PMH [postmenopausal health] market by driving urgency to prevent PMH risks." In order to achieve this objective, the Business Plan noted: "Leverage national advocacy efforts to create and build market as defined by osteoporosis, cardiovascular disease and breast cancer."

23. In or about October 1998, ELI LILLY's Evista Brand Team created and

distributed an "Evista Best Practices" videotape for a sales force meeting. Following an introduction by a member of the Evista Brand Team, the videotape features top performing sales representatives relaying their "best practices." On the videotape, an ELI LILLY salesman relayed how he marketed Evista:

> "[H]ot flashes are important issues for women, but hot flashes will not kill a woman. Hot flashes are a warning inside a woman's body that she needs to be concerned about osteoporosis, she needs to be concerned about breast cancer, and she needs to be concerned about cardiovascular disease. And by talking about what Evista does with Doctor [A] initially, that Evista truly is the best drug for the prevention of all these diseases, you can then deal with what Evista doesn't do in the negotiating standpoint and still get the majority of patients. He is to the point now, where he is prescribing about 10 prescriptions a week, about 40 a month . . ."

24. In or about the fourth quarter of 1998, ELI LILLY's Evista Brand Team disseminated an internal ELI LILLY memorandum titled "Communication Critical Success Factors" which stated with respect to Evista that:

> "differentiation is critical. Must engage in dialogue around broad profile. We have little ability to differentiate ourselves from the competition based on bone. Lack of indication of hip fracture (unlike estrogen and Fosamax) will impede bone attractiveness. Lack of interest (no urgency) in OP [osteoporosis] alone. OP profile is not easily differentiated from competition (no competitive advantage). Must understand the benefits as a package – visual proximity of all of the benefits is critical. The customer must be able to easily link all benefits. The more we downplay our broad profile the less importance to the consumer."

25. In or about October 1998, ELI LILLY ran an advertisement in *Prevention Magazine* promoting Evista. The advertisement was approved by ELI LILLY's Evista Brand Team. The advertisement declared that Evista "Prevents osteoporosis . . . Lowers cholesterol . . . Addresses concerns about breast cancer." On or about January 12, 1999, ELI LILLY received a Notice of Violation issued by the FDA, informing ELI LILLY that the advertisement violated the FDCA because it lacked fair balance, overstated Evista's benefits, presented an unsubstantiated

safety claim, and minimized Evista's risk information. With respect to the overstatement of benefit, the FDA's Notice of Violation stated: "This advertisement is misleading because it overstates Evista's benefits. By promoting 'Prevents osteoporosis . . . Lowers cholesterol . . . Addresses concerns about breast cancer' with equal prominence, this advertisement implies that Evista is indicated for a broader range of uses than supported by the product's labeling." In response to the Notice of Violation, ELI LILLY agreed in a letter to FDA not to run the advertisement again.

26. Beginning as early as May 17, 1998, and continuing thereafter until December 4, 1998, ELI LILLY sales representatives promoting Evista promoted the sale and use of Evista for Unapproved Uses in the Southern District of Indiana and elsewhere.

27. On or about May 17, 1998, an ELI LILLY District Manager responsible for ELI LILLY sales representatives promoting Evista sent an email to his multi-state sales staff entitled: "Medical Letters & May Promo List." The email stated: "lets make sure we're maximizing our resources to move share. Of note. . . the top three areas with EVISTA SOM [Share of Market] have requested THE MOST medical letters. These letters go beyond (just like NEJM [New England Journal of Medicine]) what we are able to discuss with our customers. We should be making all product medical letters available, especially . . . EVISTA (Bone, Lipid, Breast Cancer), when working to answer any AOCs [Areas of Concern]." Sales representatives were encouraged to send unsolicited medical letters to promote Evista for Unapproved Uses to doctors on their sales routes. The email sent included email recipients in more than one State.

28. As detailed below, ELI LILLY sales representatives promoting Evista met with numerous doctors and promoted Evista for Unapproved Uses. ELI LILLY sales representatives were trained to prompt or bait questions by doctors in order to promote Evista for Unapproved

Uses.

29. On or about June 12, 1998, an ELI LILLY sales representative met with a doctor in North Carolina and promoted Evista for the prevention of breast cancer.

30. On or about June 17, 1998, an ELI LILLY District Manager responsible for ELI LILLY sales representatives promoting Evista sent an email to his sales staff entitled: "Evista Audioconference." The email stated: "Just like requesting the three medical letters: Effects on Breast Tissue, Lipids and CV [cardiovascular] parameters, [and] Effects on Skeleton this is another resource that is already in place that can impact our doctors to pick up that pen NOW and write EVISTA."

31. On or about June 23, 1998, an ELI LILLY sales representative met with a doctor in Illinois and promoted Evista for the reduction in the risk of cardiovascular disease.

32. In or about the third quarter of 1998, an ELI LILLY Area Director supervising ELI LILLY District Managers responsible for sales representatives promoting Evista distributed an Executive Summary of the Area's activity for the second quarter of 1998. The Area Director's responsibility included several district offices. This memorandum, entitled "Stretching the Standard," noted that the Area ranked fourth with one other area of the country and "it is important to note that we now have only two quarters left in this year to demonstrate our ability to launch this blockbuster product and to position ourselves higher in the area rankings." An attachment to the memorandum titled "Focused Leadership Effort," stated with respect to Evista: "Ensure confidence and conviction with revised strategy and selling message through . . . Doctor Driven resources initiatives . . . Medical letters 'Big 3' (Bone, Breast, Lipids)." Sales representatives were being encouraged to send unsolicited medical letters to promote Evista for Unapproved Uses.

33. On or about August 21, 1998, an ELI LILLY sales representative met with a doctor in Illinois and promoted Evista for the reduction in the risk of breast cancer.

34. On or about September 3, 1998, an ELI LILLY sales representative met with a doctor in Texas and promoted Evista for the prevention of breast cancer.

35. No later than October 2, 1998, ELI LILLY's Evista Brand Team was provided with market research results from a survey of doctors who had recently been visited by an ELI LILLY sales representative promoting Evista. When asked, "[w]hat were the main messages you recall from the most recent Evista call," 24% of the doctors recalled receiving the message that Evista may reduce the risk of breast cancer. Six months earlier, there had been no indication that doctors recalled that Evista may reduce the risk of breast cancer. Given this shift, a Senior Project Director at Richard Day Research (a private marketing consultant company) and author of the report concluded that "[p]erception changing from 'does not increase the risk of breast cancer' to 'may reduce the incidence of breast cancer.'"

36. On or about October 7, 1998, an ELI LILLY sales representative met with a doctor in California and promoted Evista for the reduction in the risk of breast cancer.

37. On or about October 9, 1998, an ELI LILLY sales representative met with a doctor in Alabama and promoted Evista for the reduction in the risk of breast cancer.

38. On or about October 9 through 11, 1998, ELI LILLY's Evista Brand Team organized a consultant meeting entitled the "Evista Current and Future: A Market Research Summit." Among the presentations made to the physicians were "Evista and Markers of Cardiovascular Risk" and "Estrogens, Anti-Estrogens and SERMs: Impact on Breast Cancer Incidence and Implications For Prevention." During these presentations, Unapproved Uses of Evista were discussed. A post-conference survey of the physicians that attended the meeting

revealed that "Evista was rated most effective at preventing osteoporosis and reducing the risk of breast cancer."

39. On or about November 12, 1998, an ELI LILLY sales representative met with a doctor in Missouri and promoted Evista for the reduction in the risk of breast cancer.

40. On December 4, 1998, an ELI LILLY sales representative met with a doctor in Georgia and promoted Evista for the reduction in the risk of breast cancer.

41. From May 17, 1998 until December 4, 1998, ELI LILLY profited by $3.75 million dollars ($3,750,000) based on sales of Evista which was misbranded and distributed in interstate commerce.

COUNT ONE

Distribution of a Misbranded Drug
21 U.S.C. §§ 331(a) and 352(f)(1)

1. The allegations contained in paragraphs 1 through 41 are realleged and incorporated herein as if set forth in full.

2. Beginning as early as May 17, 1998, and continuing thereafter until December 4, 1998, in the Southern District of Indiana, and elsewhere, defendant

ELI LILLY

did introduce and cause the introduction into interstate commerce quantities of Evista, a drug within the meaning of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 321(g), which drug was intended for use in the prevention and reduction in the risk of breast cancer, and the reduction in the risk of cardiovascular disease, and which drug was misbranded within the meaning of 21 U.S.C. § 352(f)(1), in that Evista's labeling lacked adequate directions for such uses.

All in violation of 21 U.S.C. §§ 331(a), 333(a)(1) and 352(f)(1).

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DATE: December 21, 2005

STATE OF INDIANA)
) SS:
COUNTY OF MARION)

Christina McKee, being first duly sworn, upon her oath deposes and says that she is an Assistant United States Attorney in and for the Southern District of Indiana, that she makes this affidavit for and on behalf of the United States of America and that the allegations in the foregoing Information are true as she is informed and verily believes.

Christina McKee
Assistant United States Attorney

Subscribed and sworn to before me, a notary public, on this 21st day of December, 2005.

Sharon E. Szeszycki
Notary Public

My Commission Expires:

November 19, 2006

My County of Residence:

Hancock